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The effect of gender on the long-term course and outcome of schizophrenia in rural Ethiopia: a population-based cohort

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Abstract

Background: Although some studies have suggested that women with schizophrenia are more likely to achieve positive outcomes, the evidence-base is fraught with inconsistencies. In this study we compare the long-term course and outcomes for men and women living with schizophrenia in rural Ethiopia.

Methods: The Butajira course and outcome study for severe mental disorder is a population-based cohort study. Community ascertainment of cases was undertaken between 1998 and 2001, with diagnostic confirmation by clinicians using the Schedules for Clinical Assessment in Neuropsychiatry. Findings from annual outcome assessments were combined with clinical records, patient and caregiver report, and psychiatric assessments at 10-13 years using the Longitudinal Interval Follow-up Evaluation- LIFE chart. For the sub-group of people with schizophrenia (n=358), we compared course of illness and treatment, co-morbidity, recovery, social outcomes and mortality between men and women. Multivariable analyses were conducted modelling associations identified in bivariate analyses according to blocks shaped by our a priori conceptual framework of the biological and social pathways through which gender might influence the course and outcome of schizophrenia.

Results: Looking into over 10-13 years of follow-up data, there was no difference in functioning or recovery in women compared to men (AOR= 1.79, 95% CI=0.91,3.57). Women were less likely to report overall life satisfaction (AOR=0.22, 95% CI=0.09 ,0.53) or good quality of spousal relationships (AOR=0.09, 95% CI=0.01-1.04). Men were more likely to have co-morbid substance use and there was a trend towards women being more likely to be prescribed an antidepressant (AOR=2.38, 95% CI=0.94, 5.88). There were no gender differences in course of illness, number of psychotic episodes or adherence to medications.

Conclusion: In this rural African setting, we found little evidence to support the global evidence indicating better course and outcome of schizophrenia in women. Our findings are suggestive of a gendered experience of schizophrenia which varies across contexts. Further investigation is needed due to the important implications for the development of new mental health services in low and middle-income country settings.

Introduction

Findings across a range of different outcomes are broadly consistent with a more positive course and outcome of illness for women living with schizophrenia compared to men diagnosed with the disorder [1, 2]. There is some heterogeneity in results and this is sometimes attributed to the effect of unmeasured 'cultural' factors [3]. For example, women are more likely to achieve functional remission than men [4], have less severe clinical symptoms, including a lower level of negative symptoms [3], although women have been found be more likely to have depression [5]. The pathways to these differences in outcomes could be partly shaped by underlying biology- for example, age of onset in women is generally 3-5 years later than that for men and early onset is associated with a range of worse outcomes, including social functioning; oestrogen may facilitate the effects of antipsychotics, causing women to have a better treatment response and therefore a better course of illness [6]. However, socioculturally constructed experiences of gender are also likely to play an important role in the differential outcomes between men and women living with schizophrenia. For example, in a study with 14 years of follow-up carried out in rural China, Ran et al found that men had higher rates of divorce, living alone, fewer caregivers, and families of men living with schizophrenia had lower economic status [3]. The authors suggest that women living with schizophrenia might be more readily accepted in rural China, receiving better social support, thus mediating more positive outcomes, including fewer negative symptoms. Similarly, authors of a longitudinal study carried out in urban India suggested that difficulties faced in achieving social norms of occupational functioning were a factor in shaping worse outcomes for men living with schizophrenia, compared to women, where economic dependence was more usual and less detrimental to continuing to receive social support [7].

Study designs commonly used in high income country settings to understand the course and outcome of schizophrenia have limited utility in low and middle-income country. For example, longitudinal studies are either: incidence cohorts recruited at the time of first episode of psychotic illness [8-10], or studies which examined outcomes for inpatients discharged from specialist care settings [11, 12].. In LMIC, where the vast majority of men and women living with schizophrenia do not access biomedical health services, or do so many years after onset of illness [13], prospective studies which start early in the course of disease are not feasible: comparable studies would require large-scale community recruitment, which is uncommon [14, 15]. This has resulted in an evidence-base which consists largely of research from HIC, with limited knowledge on the course of illness in LMIC. There is an overall lack of understanding of the potential for sociocultural differences to influence outcomes, although this was noted as a possibility by researchers carrying out cross-national studies in the 1990s [16]. Research on the effects of gender in LMIC is complicated further by other methodological challenges which mean that it has been difficult to ascertain the true extent of differences between men and women in the course and outcome of schizophrenia. Research on this topic tends to be secondary data analysis, meaning that often, sample sizes of men and women are insufficient for detailed analyses [1] and there is a lack of data available on potential confounders of associations between gender and course and outcome, for example: social support, autonomy, help-seeking. Despite these difficulties, there are a few notable examples of longitudinal studies carried out in LMIC settings which have provided important contributions to the evidence-base about the potential for differences in course and outcome of schizophrenia between men and

women. This includes Ran et al (rural China, 14 years of follow-up, n=265 women, n=224 men) who found that men had lower survival, and higher rates of suicide and were more likely to be: single or divorced, or homeless compared to women [3]; as well as Gureje and Bamidele (urban Nigeria, 13 years of follow-up, n=64 women, n=56 men) who found that although women had a more benign course of illness and were more likely to be married, they were more likely to report lower frequency and quality of social contact [17, 18]. These studies notwithstanding, the vast majority of evidence about gender and schizophrenia comes from studies carried out in HIC. Given that sociocultural constructions of gender, norms of social roles of men and women and support differ across settings, the extent to which findings are generalizable outside of the context in which the studies were undertaken is uncertain.

The research presented here is the result of a comprehensive analysis of longitudinal outcomes of schizophrenia in relation to gender, using long-term follow-up data from the Butajira cohort, the only community-based long-term study of people living with Severe Mental Illness (SMI) in a low income, rural sub-Saharan African setting. This work builds upon previous analysis of data from the Butajira cohort which examined baseline cross-sectional associations with course of illness [15] and both short-term (mean= 3.4 years) [19] and longer-term outcomes (Psychiatric Status Rating, pattern of illness, mortality) [20]. Gender was not the primary focus of these studies, but several findings indicated gender differences that warranted further investigation. Although it is generally accepted that, the prevalence of schizophrenia is equal among men and women [21], among the Butajira cohort it was much higher, with men outnumbering women by a ratio of almost five to one. Authors concluded that this difference was not explained by either differential out-migration or mortality among the general population, as there were no sex differences among non-participants in the study [15, 22]. Five-year mortality for all participants living with schizophrenia was found to be six times higher than that found in the general population and higher for men than for women (6.3 versus 4.3, respectively) [23]. Over a 10-year period, although mortality was higher among men compared to women (19.3% compared to 12.9%), this difference was not statistically significant [24]. All of those who died due to suicide were male (n=9), but again, this difference was not statistically significant [20, 24]. Mental health status scores of women appeared to be slightly better than those of men with every year of follow-up [20]. In contrast with results from a recent meta-analysis [25], among the Butajira cohort, men were found to have a later age of onset of psychotic symptoms compared to women. Authors suggested that this might be due to selection bias- with only women exhibiting the most severe disorder recognized as having the disorder [15]. Other findings perhaps reflected the disadvantage of women in Ethiopian society, compounded by the presence of SMI: men living with schizophrenia were more likely to be married, better educated and employed than women living with the disorder [22].

The aim of our analyses was to investigate impact of gender/sex upon the course and outcome of schizophrenia, from the perspective of long-term follow-up of participants from a rural, low income country in a sociocultural context different from that of most published studies. As described in Figure 1, following our review of the literature, we constructed a conceptual framework which we used as the basis for analyses, separating differences in outcomes between men and women which are more likely to be driven by biological factors (e.g. those associated with sex) and those shaped by sociocultural construction (e.g. those associated with experiences of gender).

Methods

Results presented here are based on analysis of data from 10-13 years follow-up of 358 people with a diagnosis of schizophrenia from the Butajira cohort study on people living with SMI in rural Ethiopia. Study methods, including selection of measures and results from the study have been described in detail elsewhere e.g. [15, 22, 24, 26].

Setting

Butajira is a rural district of Ethiopia located 135 kilometres south-west of Addis Ababa. In 1998, at the time of initiation of the cohort, the surrounding district of Meskan and Mareko had a population of 227,135 people. The district was divided into 45 sub-districts, four of which are located in Butajira town (urban). Butajira has hosted a Demographic Surveillance Site since 1987. At the start of the cohort, there was one health centre and five health stations located in the district. A hospital was opened in Butajira in 2001. Until the initiation of the Butajira Cohort Study, in which mental health care, including medication was provided free of charge, there was no mental health care available within the district. The vast majority of people living with SMI were naïve to biomedical treatment prior to participation in the study but had commonly accessed traditional medicine for their illness [27] .

The Butajira Cohort Study

The cohort was initiated in 1998, with a door-to-door survey of adults of reproductive age (15-49 years). A two-stage screening process was used to identify people living with schizophrenia, bipolar disorder and severe major depression. Out of an estimated population of 83,282, a total of 68,378 people were screened using the Composite International Diagnostic Interview (CIDI 2.1), out of which 53.0% were female [22]. In addition, key informants from each village within the community were asked to identify people they thought might be living with SMI. This yielded 719 in total with a possible diagnosis of schizophrenia. The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) was used as the second stage of screening, resulting in 321 (54 Women and 267 men) with a diagnosis of schizophrenia [15]. Out of all subjects invited for the SCAN interview, 38.0% were female [28] . Forty additional incident cases were identified using a similar diagnostic process during the first two years of the cohort. The main advantage of the LIFE chart is that data from participants can be included up until a censor point; for example, death, refusal, loss to follow-up. For the analyses presented here, the sample size was 358 (3 participants were excluded due to missing data). The first stage of screening (CIDI) was carried out by trained interviewers (local high school graduates, employed via competitive recruitment); the SCAN was administered by medical doctors with experience in mental health care. Variables on age at first prodromal symptoms and age at first recognition of disorder were derived from the SCAN.

Follow-up data on participants was collected at monthly clinical appointments held at the research centre in Butajira town. The same project workers originally employed to carry out screening invited and supported participants to attend monthly appointments, including organising home visits where necessary. Psychiatric nurses carried out a clinical assessment at each appointment, which included: assessment of clinical state during the preceding month, presence/absence of psychotic symptoms, use of medication, whether the patient was in episode/remission at the time of the appointment; suicidality; alcohol and Khat use. Patient deaths were recorded (described as mortality in Table 2). In addition to the monthly clinical assessment, the following research instruments were administered annually: Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [29], Scales for Assessment of Positive Symptoms (SAPS), Scales for Assessment of Negative Symptoms (SANS) [30], Global Assessment of Functioning [31]. Medication (first generation psychotropics and antidepressants) was available free of charge and was prescribed according to clinical indication.

Long-term outcomes were collected in 2012 using the Longitudinal Interval Follow-up Evaluation (LIFE) chart data [32]. Validated in diverse settings, and previously used in Ethiopia, the LIFE chart is a semi-structured questionnaire, designed to be used by clinicians to effectively summarise longitudinal clinical data. Primary rating scales for the LIFE chart include the Psychiatric Status Rating (PSR), used in the Butajira cohort (and elsewhere [33, 34]) as an instrument to help clinicians capture the severity of symptoms at each monthly (or weekly) visit since enrollment: in our case enabling annual summarization of psychopathology and functional status of participants over 10-13 years of follow-up. For the Butajira study, four psychiatrists were trained in the LIFE chart approach [35].The PSR ratings were carried out using all available information: reports by patients and their caregivers following face to face interviews, family and psychiatric nurses, monthly clinical records, annual symptomatic and functional ratings, and reports from the project outreach workers who had monthly contacts with people living with severe mental disorders and their families [35]. SAPS and SANS scores are included as an input for the PSR and so only baseline SAPS and SANS scores are reported separately in our results (Table 1). Hamilton Depression Scale [36] was administered by psychiatrists or psychiatric trainees. Psychiatric Status Rating scores (where a score of 1-2 indicating remission, 3-4 suggestive of partial remission and 5-6 indicating that the participant was experiencing a psychotic episode) were used as the basis of course of illness variables: number of psychotic episodes; percentage of individual patient's follow-up time spent in remission. We developed two recovery variables: more than 6 consecutive months spent in remission and more than 12 consecutive months spent in remission. Also derived from the LIFE Chart were variables related to psychosocial functioning: interpersonal relationships (with separate ratings for spouse, children, other important relatives); social adjustment; sexual enjoyment; life satisfaction; all of which were structured as six to eight-point ordinal rating scales, with detailed descriptions of each category. For example: poor for interpersonal relationships is described as "regularly argues with family members (often not resolved), prefers avoiding contact/feels deficit in emotional closeness, derives no pleasure from contact"; whereas very good is defined as: " experiences good relationships with family members, with only transient friction, rapidly resolved, feels only minor/occasional need to improve relationship, which is close and satisfying"[32]. Carer burden and experience of stigma scores were derived from the Family Interview Schedule [37]. We also examined treatment, using the following variables: percentage of individual patient's follow-up time spent in treatment, percentage of individual patient's follow-up time spent on antipsychotics, percentage of individual patient's follow-up time spent on antidepressants, percentage medication

adherence over follow-up period: calculated using number of prescriptions recorded as the denominator and self-reported number of prescriptions collected from pharmacies as the numerator.

Analysis

The overall approach was to stratify and compare outcomes by gender. We described study participants at baseline stratified by sociodemographic characteristics and current clinical state (entry into clinical care) using proportions, chi squared and t tests. We also calculated odds ratios, where appropriate. Using variables derived from the LIFE chart data, we carried out bivariate analysis using chi-square and calculated odds ratio to examine associations between gender and the following outcomes: course of illness and treatment (recovery, time spent in remission, number of psychotic episodes, time on treatment- antipsychotic, antidepressant, adherence), co-morbidity, mortality and social outcomes (functioning, adjustment, satisfaction, employment, stigma, quality of relationships). Finally, we carried out multivariable analyses, modelling associations identified in bivariate analyses according to blocks shaped by our a priori conceptual framework of the pathways through which gender might influence the course and outcome of schizophrenia, models included: 1. proxy indicators of biological factors (baseline clinical state, age at first prodromal symptoms); 2. recovery and 3. recovery adjusted for adherence to follow-up appointments; 4. medication; 5. social outcomes. All models were adjusted for possible confounders: urban/rural residence, age at recognition of illness. Urban/rural residence was found to be associated with sex [22] and was hypothesised to have an effect upon identification of mental illness, help-seeking behaviour and access to healthcare. Similarly, age at first recognition of illness was previously found to be associated with sex [15] and expected to be associated with course of illness outcomes. Models 2,3 and 5 were adjusted for present clinical state rating at baseline and age at first prodromal symptoms. Model 4 was adjusted for baseline depressive symptoms.

Results

Three hundred and fifty-eight participants in the Butajira cohort with a diagnosis of schizophrenia and complete follow-up data were included in our analyses (62 women and 296 men, see Table 1). Women were more likely to be divorced/separated or widowed; less likely to be literate; had a younger age of onset and an earlier age of first recognition of illness. At baseline, women were more likely to be in remission and there was no gender difference in positive or negative mean symptom scores or social functioning.

Table 2. describes crude associations between gender and a range of clinical and social outcomes. There was only weak evidence that women had more positive outcomes than men in terms of being more likely to have more than 12 consecutive months in remission; being more likely to spend more than 75 percent of the time in remission. Despite no difference in symptoms of depression between men and women, women were more likely to spend a higher proportion of time on antidepressants. There was no difference in overall proportion of time spent on any treatment, but women had better adherence and were more likely than men to spend a high proportion of time (more than 75 percent) on antipsychotic medication. In terms of social outcomes: women were more likely to report lower overall life satisfaction as well as less satisfaction with spousal relationships. Men were more likely to use khat/alcohol.

Table 3. describes the results of multivariable analyses. Model 1. Shows that there was strong evidence that men were more likely to be in episode at baseline (AOR=3.41, 95% CI=1.08-10.74) and a trend towards older age at first prodromal symptoms (AOR=2.62, 95% CI=0.93-7.36). Models 2 and 3 show that after adjusting for adherence (attendance of follow-up appointments) the trend towards association of recovery with female sex disappears (AOR=0.62, 95% CI=0.30-1.27). Model 4. Demonstrates that after adjusting for baseline depressive symptoms, a trend towards women being more likely to spend a high proportion of time on antidepressants remained (AOR=0.42, 95% CI=0.17-1.06). Finally, Model 5. Shows that women generally had worse social outcomes, being less satisfied overall, less likely to be satisfied with spousal relations and more likely to be divorced/widowed.

Discussion

In our analysis of data from the Butajira cohort in rural Ethiopia, we found little evidence to suggest that women experienced more positive outcomes. There was no difference in functioning and recovery, once models were adjusted for confounders. In terms of social outcomes, specifically, overall life satisfaction and quality of spousal relationships, women had worse outcomes. This is in the context of much higher khat/alcohol use among men and more time spent on antidepressants by women, despite similar levels of depressive symptoms between men and women (at baseline).

The patterns of both prevalence and age of onset among men and women found among the Butajira cohort are in contrast to those found in the majority of studies from both high and low and middle-income settings. For example, the most recent analysis of Global Burden of Disease data found no sex difference in prevalence and no evidence to support the development of schizophrenia at a later age among women [21]. A key potential limitation to the robustness (and generalisability) of our findings is the extent to which men and women living with schizophrenia included in the study may be considered representative of people living with the disorder in the Butajira community. The community-based design is a key strength in a setting where the vast majority of people living with SMI were naïve to biomedical treatment before the initiation of the study. The design is unusual, particularly when compared to other longitudinal studies carried out in sub-Saharan Africa, which have tended to be clinic-based [17, 38]. Although we adjusted final models for age of onset to adjust for selection bias, it is unlikely that this was fully effective in controlling for differential entry into the cohort by men and women. A possible explanation is, that in this setting, only women exhibiting the most severe symptoms are commonly recognized as having schizophrenia. Alternatively, patterns of arranged marriage in which women have little autonomy, marry young and move away from their families may provide a trigger for early onset or earlier recognition of symptoms [22]. Further research is required to understand the true nature of the observed association between being female and early onset in this setting. The small number of female participants poses a practical challenge to robust analysis. Insufficient power to detect a difference in outcomes cannot be ruled out as an explanation for our findings. There was no standardized measure of adherence: this was based on self-reported collection of prescriptions- this measure is therefore subject to recall and social desirability bias. Women were treated with antidepressant medications more than men during the follow-up period. There was no significant between group difference in the negative symptoms score at baseline, and ratings were completed by trained psychiatrists who could reasonably be expected to be able to differentiate between negative and depressive symptoms. Therefore, the higher proportion of time that women spent on

antidepressant medications can fairly be attributed to depressive symptoms rather than negative symptoms of schizophrenia.

Our research contributes to a small evidence-base which examines differences in social outcomes between men and women living with schizophrenia in LMIC. It should be noted that the global evidence-base is equivocal, with a recent meta-analysis showing no difference in recovery (defined as improvements in both clinical and social domains and evidence that improvements in at least 1 of these 2 domains had persisted for at least 2 years)[39]. Only 5 of the 50 studies included in this meta-analysis came from a low income country setting: it seems likely that differences may be more prominent in some LMIC settings where social norms linked to life expectations and indications of success are arguably more strongly gendered. In an early study carried out in Nigeria which used review of clinical records to assess outcomes over time, men had better social adjustment [38]. In their 13-year follow-up study of outpatients in an urban centre in South-West Nigeria, Gureje and Bamidele noted that in their sample, women exhibited a greater degree of impairment in terms of frequency and quality of social contact. Although women were more likely to have ever married, data about the quality and nature of marriage and spousal relationships was not collected in this study [17] . However, it seems possible that women's illness may be either less apparent at the younger age at which they are expected to get married or, alternatively, that their symptoms are more easily concealed, which may be desirable given the stigma with which they are associated [40]. In India, it was suggested that, whereas women were likely to be blamed for not conceiving or performing caregiving and homemaking duties effectively (responsibilities only taken on after marriage); men were blamed for their inability to hold down a stable job (a likely criterion for getting married) [41]. In contrast, in two year follow-up study conducted in rural China, the authors suggested that more positive clinical outcomes among women could be attributed to women living with schizophrenia being more able to perform their expected role- housework, childcare and some farm-work and that this social functioning helped to prevent clinical deterioration [42]. Given that we understand that gender roles, expectations and experiences are culturally mediated and that together they exercise a strong influence upon health and illness, it is to be expected that experience of living with schizophrenia will be mediated by sociocultural constructions of gender. We should therefore anticipate gendered differences in outcome, with variation in different sociocultural contexts. These differences have important implications for both future research and development of new services and are currently neglected.

Recognition of the importance of gender in SMI research in LMIC will be needed to ensure that studies are designed in such a way as to: generate robust estimates for differences in outcomes; understand the determinants of these. Like other similar studies, ours was potentially under-powered to detect and investigate differences by gender. Efforts should be made to ensure sufficient sample sizes to support multivariable analyses to robustly analyse gender differences. Case-finding strategies to identify women living with schizophrenia who may be "hidden" may be necessary: for example, snowball sampling among health service providers, religious and traditional healers, other key informants in communities may be needed to achieve a representative sample [43]. Prior to this, qualitative research would contribute to improved understanding of potential reasons for differential inclusion in a community-based study: to explore whether idioms of distress, explanatory models of illness (of the person living with schizophrenia, their families and the community) and the nature of the clinical/research encounter vary according to gender. Results of this kind of work would help us to understand whether the unusual pattern of age of onset and

prevalence represent a ‘true’ but unexplained difference or are a result of social construction which potentially risks inhibiting equality of access to services among men and women. This will be a necessary component of research around the design, implementation and scale-up of new mental health services in LMIC. These services will inevitably be task-shared, with much of the mental health care delivered by non-specialists [44-46]. Training which is adapted to the local context will be essential if these services are to be equitable [47, 48] .

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Table 1. Associations with baseline sociodemographic and clinical characteristics

Characteristic		Female	Male	Chi-squared (t where indicated)	P-Value	OR (95% CI) (men= comparison group)_
		62 (17.3)	296 (82.7)			
Sociodemographic						
Age in years	< 20	11 (17.7)	16 (5.5)			Ref
	20-29	20 (32.3)	116 (40)			0.26 (0.10-0.64)
	30-39	20 (32.3)	109 (37.6)			0.27 (0.15-0.68)
	40+	11 (17.7)	49 (16.9)	11.16 (df=3)	**0.01**	0.34 (0.11-0.93)
Marital status	Single	32 (51.6)	170 (57.4)			Ref
	Married	14 (22.6)	91 (30.7)			0.82 (0.41-1.61)
	Divorced/separated	11 (17.7)	30 (10.1)			1.95 (0.88-4.31)
	Widowed	5 (8.1)	5 (1.7)	11.52 (df=3)	**0.01**	5.31 (1.41-20.0)
Residence	Urban	21 (33.9)	66 (22.3)			Ref
	Rural	41 (66.1)	230 (77.7)	3.73 (df=1)	**0.05**	0.56 (0.31-1.02)
Education	Non-literate	44 (71.0)	145 (50.3)			Ref
	Literate	18 (29.0)	143 (49.7)	8.73 (df=1)	**<0.01**	0.41 (0.23-0.76)
Onset of disorder						
Age at first prodromal symptoms	15 years or less	29 (48.3)	85 (32.8)			Ref
	16-24	20 (33.3)	85 (32.8)			0.24 (0.14-0.38)
	>25	11 (18.3)	89 (34.4)	7.28 (df=2)	**0.03**	0.12 (0.07-0.23)
Age at first recognition of disorder	15 years or less	11 (18.6)	18 (6.6)			Ref
	16-24	29 (49.2)	127 (46.5)			0.37(0.16-0.89)
	>25	19 (32.2)	128 (46.9)	10.50 (df=2)	**0.01**	0.24 (0.10-0.61)
Clinical state at entry into care						
Entry duration of illness	<2 years	14 (23.3)	63 (24.2)	0.02 (df=1)	0.88	0.95 (0.49-1.85)
Psychiatric Status Rating (PSR)	Remission	8 (13.0)	10 (3.4)			Ref
	Partial remission	5 (8.1)	52 (17.5)			0.12 (0.03-0.51)
	In episode	49 (79.0)	234 (79.1)	17.16 (df=2)	**<0.01**	0.26 (0.10-0.71)
Positive symptoms score (n=316)	Mean score	6.2 (4.8-7.6)	6.4 (5.9-7.0)	t=-0.36 (df=314)	0.72	-0.002 (-0.01-0.01)
Negative symptoms score (n=316)	Mean score	12.96 (10.56-15.37)	12.52 (11.70-13.40)	t=0.40 (df=314)	0.69	0.001 (-0.001-0.23)
Social functioning (GAF)	Mild/minimal impairment	5 (8.1)	12 (4.0)	1.82 (df=1)	0.18	0.48 (0.16-1.43)

Table 2. Associations with clinical and social outcomes

Characteristic		Female	Male	Chi-squared	P-Value	OR (95% CI) (men= comparison group)_
Course of illness						
Recovery (>12 consecutive months in remission)		17 (27.9)	58 (20.0)	2.09 (df=1)	**0.15**	1.58 (0.84-2.98)
Recovery (>6m consecutive months in remission)		40 (65.6)	172 (58.1)	1.17 (df=1)	0.28	1.37 (0.77-2.45)
Percent time spent in remission	<25	28 (45.2)	172 (58.1)			Ref
	25-49	10 (16.1)	36 (12.2)			0.37 (0.16-0.89)
	50-74	6 (9.7)	37 (12.5)			0.24 (0.10-0.61)
	>75	18 (29.0)	51 (17.2)	6.21 (df=3)	**0.10**	2.17 (1.10-4.27)
Treatment						
% time in treatment	<25	21 (33.9)	129 (43.6)			Ref
	25-49	14 (22.60)	65 (22.0)			1.32 (0.63-2.78)
	50-74	10 (16.1)	45 (15.2)			1.37 (0.60-3.13)
	>75	17 (27.4)	57 (19.3)	2.84 (df=3)	0.42	1.83 (0.89-3.75)
% time on antipsychotic	<25	34 (54.8)	174 (58.8)			Ref.
	25-49	13 (21.0)	53 (17.9)			1.30 (0.65-2.59)
	50-74	5 (8.1)	53 (17.9)			0.45 (015-1.35)
	>75	10 (16.1)	23 (7.8)	6.29 (df=3)	**0.10**	2.21 (0.96-5.11)
% time on antidepressant	<25	50 (80.7)	270 (91.2)			Ref.
	25-49	2 (3.2)	13 (4.4)			0.83 (0.18-3.80)
	50-74	3 (4.8)	6 (2.0)			2.70 (0.65-11.23)
	>75	7 (11.3)	7 (2.4)	12.86 (df=3)	**0.01**	5.40 (1.78-16.40)
Medication adherence	<25%	12 (19.4)	63 (21.3)			Ref
	25-49%	9 (14.5)	47 (15.9)			1.01 (0.39-2.59)
	50-75%	12 (19.4)	62 (20.9)			1.02 (0.42-2.44)
	>75%	28 (45.2)	116 (39.2)			1.27 (0.60-2.67)
	Not prescribed	1 (1.6)	8 (2.7)	0.91 (df=4)	0.92	0.66 (0.07-5.83)
Adherence to follow up appointments	<25%	14 (22.6)	82 (27.7)			Ref
	25-49%	4 (6.5)	48 (16.2)			0.49 (0.15-1.58)
	50-75%	15 (24.2)	63 (21.3)			1.39 (0.62-3.11)
	>75%	29 (46.8)	103 (34.8)	6.1 (df=3)	**0.11**	1.65 (0.81-3.34)
Social outcomes						
Social functioning (GAF)	Mild/ minimal impairment	21 (33.9)	88 (29.7)	0.66 (df=2)	0.72	1.21 (0.68-2.17)
Social adjustment	Fair-very good	27 (43.5)	108 (36.5)	1.09 (df=1)	0.30	1.34 (0.77-2.34)
Satisfaction	Fair-very good	45 (72.6)	250 (84.5)	4.99 (df=1)	**0.03**	0.49 (0.26-0.93)
Mean stigma score	0	6 (9.8)	38 (13.6)			Ref
	0-1	36 (59.0)	176 (63.1)			1.30 (0.51-3.30)
	>1	19 (31.2)	65 (23.3)	1.94 (df=2)	0.38	1.85 (0.67-5.09)
Mean carer burden score	0	11 (18.0)	52 (18.6)			Ref
	0-1	12 (19.7)	75 (26.7)			0.76 (0.31-1.85)
	1-2	17 (27.9)	74 (26.5)			1.09 (0.47-2.52)
	2-3	21 (34.4)	78 (28.0)	1.78 (df=3)	0.62	1.27 (0.56-2.87)
Quality of relationships						
Parents	No relationships	24 (38.7)	102 (34.5)			Ref
	Fair-very good	32 (51.6)	153 (51.7)	0.94 (df=2)	0.62	0.89 (0.49-1.60)
Siblings	No relationships	4 (6.5)	10 (3.4)			Ref
	Fair-very good	48 (77.4)	231 (78.0)	1.41 (df=2)	0.49	1.14 (0.54-2.40)
Spouse	No	51 (82.3)	190 (64.2)			Ref

	relationships					
	Fair- very good	11 (17.7)	98 (33.1)	8.1 (df=2)	**0.02**	0.42 (0.21-0.84)
Children	No relationships	33 (53.2)	168 (56.8)			Ref
	Fair- very good	27 (43.5)	114 (38.5)	0.70 (df=2)	0.70	1.21 (0.69-2.12)
Friends	Poor	165 (83.3)	131 (81.9)			Ref
	Fair- very good	33 (53.2)	165 (55.7)	0.13 (df=1)	0.72	1.11 (0.64-1.92)
	No relationships	0 (0)	0 (0)			
Co-morbidity and mortality						
Hamilton Depression scale	<8	44 (71)	218 (73.6)			Ref
	9-15	8 (12.9)	39 13.2)			1.23 (0.59-2.58)
	16-22	0 (0)	3 (1.0)			0.86 (0.10-7.36)
	>23	10 (16.1)	36 (12.2)	1.3 (df=3)	0.73	1.36 (0.62-2.95)
Alcohol/khat abuse		3 (4.8)	114 (38.5)	26.4 (df=1)	**<0.01**	
Suicide attempt(s)		12 (19.4)	35 (11.8)	2.5	**0.11**	1.79 (0.87-3.70)
Mortality	Deceased	8 (12.9)	57 (19.3)	1.4	0.24	0.62 (0.28-1.38)

Table 3. Multivariate analyses

Model	Explanatory variable	Category	AOR (95% CI)	P-value
Model 1. Biological factors	Baseline present state rating	Remission	1.00	
		Partial remission	0.11 (0.03-0.48)	<0.01
		In episode	0.29 (0.09-0.93)	0.04
	Age at first prodromal symptoms	<15	1.00	
		16-24	0.78 (0.34-1.79)	0.56
		>25	0.38 (0.14-1.08)	0.07
Model 2. Recovery	Recovery	Less than 12m continuous remission	1.00	
		At least 12m continuous remission	1.79 (0.91-3.57)	0.09
Model 3. Recovery + adherence to follow-up appointments	Recovery	Less than 12m continuous remission	1.00	
		At least 12m continuous remission	1.61 (0.79-3.33)	0.19
	Adherence to follow-up appointments	<25%	1.00	
		25-49%	0.37 (0.10-1.43)	0.15
		50-75%	1.35 (0.56-3.23)	0.50
		>75%	1.27 (0.56-2.86)	0.57
Model 4. Medication	Time on antipsychotics	<75%	1.00	
		>75%	2.33 (0.78-6.67)	0.13
	Time on antidepressants	<75%	1.00	
		>75%	2.38 (0.94-5.88)	0.07
Model 5. Social outcomes	Overall satisfaction	Poor- very poor	1.00	
		Fair-very good	0.22 (0.09-0.53)	<0.01
	Marital status at endline	Single	1.00	
		Married	3.85 (0.35-1.00)	0.27
		Separated/divorced	3.03 (1.28-7.14)	0.01
		Widowed	1.49 (3.13-100.00)	<0.01
	Quality of spousal relationship	No relationship	1.00	
		Fair-very good	0.09 (0.01-1.04)	0.05
	Satisfaction with sexual relations	Dissatisfied	1.00	
		No information given	2.86 (0.76-10.0)	0.12
		Satisfied	4.35 (1.25-14.29)	0.02
	Employment	Yes	1.00	
		No- psychopathology	0.74 (0.35-1.54)	0.42
		No- other reason	6.25 (0.91-50.00)	0.06
All models adjusted for urban/rural residence; age at recognition of illness Models 2, 3 & 5 also adjusted for baseline present state rating; age at first prodromal symptoms Model 4 also adjusted for baseline depressive symptoms				

Figure 1. Conceptual framework: possible associations of female sex and female gender with course and outcomes of schizophrenia in LMIC settings